REMARKS

Reconsideration and withdrawal of any rejections of the application, and allowance of the claims, especially in view of the remarks made herein, are respectfully requested.

I. STATUS OF THE CLAIMS

Claims 47-65 are pending in the application. Claims 47 and 53 have been amended, without prejudice, without admission, without surrender of subject matter, and without any intention of creating any estoppel.

No new matter is added.

It is respectfully submitted that the claims herewith and the claims as originally presented are and were in full compliance with the requirements of 35 U.S.C. §§101, 102, 103 and 112. The changes to these claims, and remarks concerning these claims, as presented herein, were not made for the purpose of patentability within the meaning of 35 U.S.C. §§ 101, 102, 103 or 112; but rather for clarification and to round out the scope of protection to which the Applicant is entitled.

Support for the amended recitations is found throughout the specification and from the originally filed claims.

II. THE REJECTIONS UNDER 35 U.S.C. § 112, 1ST PARAGRPH ARE OVERCOME

Claims 47-65 are rejected under 35 U.S.C. 112, first paragraph, for allegedly containing a disclosure which does not reasonably provide enablement for increasing CD45 low cells by other methods or for isolating non-human CD45 low cells. Claims 47-65 are also rejected under 35 U.S.C. 112, first paragraph for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. Applicants respectfully traverse both rejections, which will be jointly addressed.

The claims are directed to a method of "increasing the relative number of CD45 low cells in a cell population, wherein the population includes committed hemopoietic cells comprising CD45 antigen, which method comprises: (i) contacting the cell population with an agent that operably engages said committed cells; and (ii) incubating committed cells that are engaged by

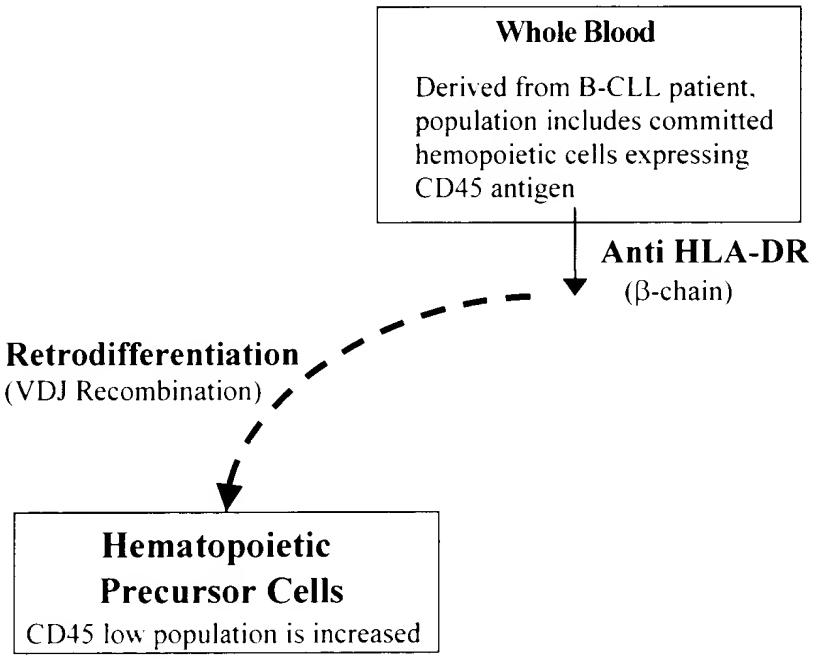
said agent such that the relative number of CD45 low cells increases as a result of said engaging."

The Examiner acknowledges that the specification is "enabling for increasing the relative number of CD45 low cells by incubating a population with an antibody to DR β-chain" and references the supporting disclosure in the specification. Accordingly, the specification provides ample support for enablement of the pending claims.

The following experiment, as described in the specification, shows the retrodifferentiation of committed blood cells to undifferentiated cells:

> All human leukocytes are CD45$^+$. Undifferentiated cells are CD45 low. Treatment of blood samples with monoclonal antibody to the homologous region of the chain of the HLA-DR antigen increased the relative number of CD45 low cells, which coincided with a decrease in the relative umber of CD45 high cells, indicating that B cells were retrodifferentiating into undifferentiated cells. *See* the Specification, page 28. The appearance of the undifferentiated cells occurred over time. *See* the Specification, page 29 (Table 6 shows the results of patient numbers 2, 3 and 4 which represent samples analyzed from the same patient over time).

Blood Sample	+	Anti HLA - DR	=	Undifferentiated Cells
Mixed Population		mAb to *β*-chain		CD45 low



Practicing the claimed methods does not require undue experimentation.[1] A skilled artisan would readily understand how to make and use the invention to increase the relative number of CD45 low cells from a starting cell population that includes committed hemopoietic cells expressing the CD45 antigen.

As shown in the excerpt above and in the working examples throughout the specification, extensive guidance is provided to one skilled in the art, minimizing experimentation and increasing success.

The Examiner has already acknowledged that the specification is enabling for "increasing the relative number of CD45 low cells by incubating a population with an antibody to DR β-chain." This recitation is the essence of the pending claims.

Provided the details of the specification, a skilled artisan would be able to increase CD45 low cells by selecting from among any one of the antibodies and growth factors disclosed in the instant application. *See* the Specification pages 19 and 20. The level of skill in the art is high, and the teaching detailed, so that a variety of suitable agents can be employed without undue experimentation.

The Examiner states that the specification is not enabling for isolating non-human CD45 low cells, and that since HLA antigens are present only in humans, there is no evidence that the practice of the claimed invention was conceived in any other species. The Examiner recognizes that "HLA is well known in the art to be the designation of the group of antigens which comprise the major histocompatibility complex (MHC) in the human." In addition, it is well-known in the

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[1] According to the Court of Appeals for the Federal Circuit in the case of *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988),

> Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. 'The key word is undue, not experimentation.' The determination of what constitutes undue experimentation in a given case requires the application of standard of reasonableness, having due regard for the nature of the invention and the state of the art. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed ... .
> *Id.* at 1404.

Determining whether undue experimentation is required to practice a claimed invention turns on weighing many factors, for example, (1) the quantity of experimentation necessary; (2) the amount of direction or guidance presented; (3) the presence or absence of working examples of the invention; (4) the nature of the invention; (5) the state of the prior art; (6) the relative skill of those in the art; (7) the predictability or unpredictability of the art; and (8) the breadth of the claims. *Id.*

art that orthologous groups of antigens are found in other organisms besides humans, and that in some cases these orthologs have 76-78% identity with the human antigens. Antibodies recognizing antigens such as these are known in the art and available for use in carrying out the claimed methods (*See* http://www.keithbajhat.com/abvxr/chimp.html, print out attached).

It would be a matter of routine optimization for the skilled artisan to employ the claimed methods in a species that has such identity with human MHC and to successfully increase the relative numbers of CD45 low cells. The working knowledge of antibodies and immunology of a skilled artisan would enable them to apply the present invention to another species without undue experimentation.

To demonstrate the close relationship between the MHC of humans and other species, the Examiner will find attached several relevant abstracts showing the available public knowledge of orthologs in mice corresponding to human HLA-DM and HLA-DO (Alfonso and Karlsson), the high identity between specific human and rabbit MCH class II antigens (Hermel et al.), the similarities in expression and function between regions of the swine histocompatibility complex and that of humans (Ando et al.), as well as the identification of six genes in zebrafish which are known to be linked to the MHC class II region in mice and humans (Sultman et al.).

The Examiner states that the claims as filed are drawn to a "method of increasing the number of CD45 low cells in a population of cells which includes CD45 positive committed hematopoietic cells, includes in scope said increase in non-human cell populations and any method of engaging hematopoietically committed cells." As previously stated, the Examiner maintains that the written description is insufficient for isolating non-human CD45 low cells since HLA antigens are present only in humans, which allegedly provides evidence that the full scope of the claimed invention was not in the Applicants' possession at the time of filing.

Determining whether the written description requirement is satisfied requires reading the disclosure in light of the knowledge possessed by a skilled artisan.[2] Such knowledge can be

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[2] The written description requirement is described by *In re Edwards*, 568 F.2d 1349 (C.C.P.A. 1970). According to *Edwards*, the function of the written description requirement is to:

> [E]nsure that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by him; to comply with the description requirement, it is not necessary that the application describe the claimed invention in *ipsis verbis*; all that is required is that it reasonably convey to persons skilled in the art that, as of the filing date thereof, the inventor had possession of the subject matter later claimed by him.
> (*Id.* at 1351-52) (emphasis added).

established by reference to patents and publications available to the public prior to the filing date of the application. As shown here above, the disclosure of the instant application is sufficient to allow a skilled artisan to practice variations of the method and/or to do so on non-human cell populations. As shown in the accompanying abstracts, many non-human cells have an MHC counterpart that can be targeted by a suitable agent to undergo retrodifferentiation into a CD 45 low phenotype. Having this knowledge at the time of filing, the inventor was in possession of the full scope of the invention.

In addition, U.S. Patent 6,090,625, (the '625 patent) also in the name of Abuljadayel, was issued on July 18, 2000, and has the same priority date as the instant application. The '625 patent was filed with the same disclosure as the instant application, and the claims that were deemed allowable are of the same scope as those currently before the Examiner. It is respectfully submitted that not only does this demonstrate sufficient knowledge in the art for a skilled artisan to practice the current invention and variations thereof, but it also provides precedent for allowance of claims of the same scope as those presented herein.

Consequently, in view of the remarks herein, it is respectfully requested that the rejections be reconsidered and withdrawn.

III. THE REJECTION UNDER 35 U.S.C. §112, 2ND PARAGRAPH IS OVERCOME

Claims 47-65 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The rejection is respectfully traversed.

Amended claims 45 and 53 are definite. Consequently, reconsideration and withdrawal of the rejection is respectfully requested.

CONCLUSION

In light of the amendments and remarks made herein, it is respectfully submitted that the application is now in condition for allowance. Early and favorable reconsideration of the application, reconsideration and withdrawal of the rejections of the application, and prompt issuance of a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

47. (Amended) A method of increasing the relative number of CD45 low cells in a cell population, wherein the population includes [including] committed hemopoietic cells comprising CD45 antigen, which method comprises:

(i) contacting the cell population with an agent that operably engages said committed cells; and

(ii) incubating committed cells that are engaged by said agent such that the relative number of CD45 low cells increases as a result of said engaging.

53. (Amended) The method according to claim 47 wherein the CD45 low [CD3 negative DR negative] cells are Major Histocompatibility Complex (MHC) class I^- and/or MHC class II^+ cells.

Antibodies that cross-react with antigens in the...

Chimpanzee

Antigen	Manufacturer	Clone	Comments
CD2	BD	S5.2	
CD3	BD	SK7	
CD3	Dako	UCHT1	
CD3	Serotec		MCA1483F
CD4	BD	SK3	
CD4	Dako	MT310	
CD8	BD	SK1	
CD8	Dako	DK25	
CD9	Dako	P1/33/2	
CD11b	BD	D12	
CD11c	BD	S-HCL-3	
CD20	BD	L27	
CD20	Dako	B-Ly 1	
CD28	BD	L293	
CD29	Coulter	4B4LDC9LDC8	
CD29	Dako	K20	
CD38	BD	HB-7	
CD45	Dako	2B11	
CD45RA	BD	L48	
CD45RO	BD	UCHL-1	
CD69	BD	L 78	
CD122	BD		
HLA-DR	BD	L243	
HLA-DR	Dako	CR3/43	
IFN-g	Pharmingen	4SB3	Stimulated cells
IL-2	Pharmingen	MQ1-17H12	Stimulated cells
IL-4	Pharmingen	8D4-8	Stimulated cells

Please forward any helpful hints, insights, opinions, or random insults to:

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[Back to Introduction]

1: Annu Rev Immunol 2000;18:113-42

Nonclassical MHC class II molecules.

Alfonso C, Karlsson L.

The R.W. Johnson Pharmaceutical Research Institute, San Diego, California 92121, USA.

Major histocompatibility complex (MHC) class II molecules are cell surface proteins that present peptides to CD4(+) T cells. In addition to these wellcharacterized molecules, two other class II-like proteins are produced from the class II region of the MHC, HLA-DM (DM) and HLA-DO (DO) (called H2-M, or H2-DM and H2-O in the mouse). The function of DM is well established; it promotes peptide loading of class II molecules in the endosomal/lysosomal system by catalyzing the release of CLIP peptides (derived from the class II-associated invariant chain) in exchange for more stably binding peptides. While DM is present in all class II- expressing antigen presenting cells, DO is expressed mainly in B cells. In this cell type the majority of DM molecules are not present as free heterodimers but are instead associated with DO in tight heterotetrameric complexes. The association with DM is essential for the intracellular transport of DO, and the two molecules remain associated in the endosomal system. DO can clearly modify the peptide exchange activity of DM both in vitro and in vivo, but the physiological relevance of this interaction is still only partly understood.

Publication Types:
- Review
- Review, Academic

PMID: 10837054 [PubMed - indexed for MEDLINE]

1: Anim Genet 2001 Apr;32 (2):73-7

Online

cDNA cloning and genetic polymorphism of the swine major histocompatibility complex (SLA) class II DMA gene.

Ando A, Kawata H, Murakami T, Shigenari A, Shiina T, Sada M, Tsuji T, Toriu A, Nakanishi Y, Mitsuhashi T, Sekikawa K, Inoko H.

Department of Molecular Life Science, Tokai University School of Medicine, Bohseidai, Isehara, Kanagawa, Japan.

cDNA clones corresponding to the swine histocompatibility complex (SLA: swine leucocyte antigen)-DM alpha chain were isolated using the polymerase chain reaction (PCR) products from the third exon in the human HLA-DMA gene as a probe. Amino acid comparative analysis revealed that these clones were more closely related to the bovine and human DMA genes than to the other swine class II genes alpha chain genes, DRA, DQA and DOA. These results suggest that the SLA-DMA gene is expressed and may function, like HLA-DM, as an important modulator in class II restricted antigen processing in swine. Furthermore, based on the sequences and PCR-restriction fragment

length polymorphism (PCR-RFLP) patterns in the SLA-DMA gene, no allelic variation was recognized in the second exon, but five allelic variations were recognized in the third exon in five different breeds of swine. These DMA alleles were defined by variation at four nucleotide positions. Two of these alleles resulted in an amino acid substitution. These results suggest that SLA-DMA has little polymorphism as observed in HLA-DMA and mouse H2-Ma.

PMID: 11421941 [PubMed - indexed for MEDLINE]

1: Immunogenetics 1999 Apr;49 (4):295-302

Related Articles, Nucleotide, Protein.
NEW Books, LinkOut

Immuno-genetics

Isolation and mapping of the rabbit DM genes.

Hermel E, Han M, Hague B, Kindt T, Monaco JJ.

Department of Molecular Genetics, University of Cincinnati, Cincinnati, OH 45267-0524, USA. ehermel.ucs@smtp.usi.edu

Proper peptide presentation by major histocompatibility complex (MHC)-encoded class II antigens is dependent on the products of the MHC DM loci. We identified the rabbit orthologues (RLA-DMA and -DMB) of human HLA-DMA and -DMB and found that they have 76.9% and 78.8% identity with HLA-DMA and -DMB, respectively. Like classical class II MHC genes, RLA-DM genes are more closely related to human HLA-DM genes than to mouse H2-DM. Among the DM family, there is a high degree of variability at the amino terminus of the DMa chains, and length variability in the cytoplasmic tails of both DMalpha and DMbeta. The rabbit DM genes are coexpressed with class II genes in lymphoid tissues, as are the DM genes of other mammals. The RLA-DM locus maps to the class II region of the rabbit MHC, and is flanked by the DP and DOB loci. Despite having some similarities to class II genes of bony fishes, the DM family represents a separate branch of the MHC class II family.

PMID: 10079293 [PubMed - indexed for MEDLINE]

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1: Scand J Immunol 2000 Jun;51 (6):577-85

Related Articles, Nucleotide, Protein, NEW Books, LinkOut

Online

Identification of seven genes in the major histocompatibility complex class I region of the zebrafish.

Sultmann H, Murray BW, Klein J.

Max-Planck-Institut fur Biologie, Abteilung Immungenetik, Tubingen, Germany.

Physical linkage of genes whose products are involved in similar physiological pathways may have functional significance. The identification of conserved gene linkage in distantly related organisms can therefore strengthen the hypothesis of selection acting towards keeping genes on a chromosome. We used the cDNA selection technique and the polymerase chain reaction (PCR) with generic primers for the identification of new genes on the genomic clones bearing the major histocompatibility complex (Mhc) class I genes of the zebrafish (Danio rerio). We found six new genes (BING1, DAXX, TAPBP, KNSL2, TAP2B and KE6) whose orthologues are known to be linked to the Mhc class II region in humans and mice. In addition, a new zebrafish Mhc class I gene, termed Dare-UFA, was detected. By contrast, a search for the human leucocyte antigen (HLA)-linked BING3, KE3 and SACM2L genes revealed that these loci are not located on the class I clones of the zebrafish. The zebrafish class I region contains repetitive elements with similarity to the DANA, SATA and LINE repeats, as well as Tc1 transposable elements. Our findings indicate a high degree of linkage conservation between the zebrafish class I and the mammalian class II regions.

PMID: 10849368 [PubMed - indexed for MEDLINE]